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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/738,404	12/17/2003	Philip E. Thorpe	3999.002587	8707

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PEREGRINE PHARMACEUTICALS, INC.
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HOUSTON, TX 77056

EXAMINER	
JOYCE, CATHERINE	
ART UNIT	**PAPER NUMBER**
1642	

MAIL DATE	DELIVERY MODE
09/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/738,404	THORPE ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-12,25,29-31,34-39,41,42 and 46-51* is/are pending in the application.

4a) Of the above claim(s) *36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-12,25,29-31,34,35,41,42 and 46-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Amendment filed June 18, 2007 in response to the Office Action of December 15, 2006 is acknowledged and has been entered. Claims 1-2, 13-24, 26-28, 32-33, 40, and 43-45 have been canceled, claims 3-12, 25, 29-31, 34-39, 41-42, and 46-51 are pending, claims 36-39 are withdrawn from examination as being drawn to a non-elected invention, and claims 3-12, 25, 29-31, 34-35, 41-42, and 46-51are currently being examined.

2. The following rejections are being maintained:

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 3-6, 8, 9-12, 25, 41-42 and 46-51 remain rejected under 35 USC 103, first paragraph, for the reasons set forth previously in the Paper mailed December 15, 2006, Section 10, pages 10-17.

Applicant argues that the rejection is overcome by amending the claims to overcome the previously stated rejection of the claim to a priority April 28, 1999 (filing date of provisional application 60/131432), and thus establish a priority date of April 28, 1999 and removing Brekken as prior art.

This argument has been considered but has not been found to be persuasive because the amendment of the claims to recite "wherein said enzyme is an enzyme set free by necrotic processes" does not establish the priority date as being April 28, 1999 because, as set forth in the previous Office Action, the disclosure of a method for treating cancer comprising administering to an animal (i) a first immunoconjugate that comprises a cleavage agent or enzyme operatively attached to at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof that binds to substantially the same epitope as the monoclonal antibody 2C3 and (ii) subsequently administering to the animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to the antibody, thereby releasing a substantially active drug specifically within the vasculature or stroma of the tumor is not found in the prior filed application.

Applicant further argues that Melton teaches that an antigen targeted by an ADEPT antibody should not circulate at "particularly high" levels as this will act as a competitor for antibody binding and that high blood levels of VEGF are known to be associated with various cancers, including breast, gastric, lung and colorectal cancers (citing Jinno et al., J. Gastroenterol., 33(3):376-82, 1998). Thus Applicants argue that the prior art teaches away from the invention. Applicant further argues that Presta concerns the humanization of the A.4.6.1 antibody and shows the humanized version to behave as A.4.6.1 and that it is documented in numerous publications prior to Presta, and is well known in the art, that the A.4.6.1 antibody binds only to free VEGF and does not bind to VEGF docked in any receptor. Applicant further argues that the addition of Brekken does not rescue the rejection because the only binding property of the 2C3 antibody described in Brekken is that it blocks VEGF binding to the VEGF receptor KDR/Flk-1 (VEGF receptor 2, VEGFR2) and that Brekken also fails to describe an antibody that can bind to VEGF when VEGF is bound to a receptor. Applicant further argues that claim 49 does not recite localization to tumor stroma, but only to tumor vasculature, and that Claim 51 emphasizes the use of an immunoconjugate that binds to VEGF bound to the VEGF receptor VEGFR1 on endothelial cells of the tumor vasculature, thereby localizing the immunoconjugate to the tumor vasculature.

Applicant's arguments have been considered but have not been found to be persuasive. Particularly, Melton teaches that circulating antigen may be problematic only if levels are "particularly high" and Jinno teaches that while elevated levels of VEGF were found in hepatocellular carcinoma, sharply elevated levels of VEGF were only found in metastatic disease. Further, Applicants arguments with regard to Presta are not found to be persuasive because Presta is cited only for the proposition of a reasonable expectation of success with anti-VEGF therapies that inhibit the action of VEGF, wherein Presta teaches such success. The suggestion for a combination of an ADEPT therapy with an anti-VEGF therapy comes from Brekken which teaches, as set forth in the previous Office Action, that the anti-VEGF antibody, 2C3, localizes strongly to connective tissue in tumors after injection into mice bearing human tumor xenografts,

that biotinylated 2C3 produced intense staining of connective tissue surrounding the vasculature of the H358 human NSCLC tumor after i.v. injection, and that endothelial cells in vessels not surrounded by storma, such as vessels running through nests of tumor cells themselves were stained in some cases. Further, in view of the above stated teaching of Brekken, Applicants arguments with regard to claims 49 and 51 and the lack of a suggestion for the targeting to tumor vascular and endothelial cells are not found to be persuasive.

5. Claims 7, 29-31, and 34-35 remain rejected under 35 USC 103, first paragraph, for the reasons set forth previously in the Paper mailed December 15, 2006, Section 11, pages 18-20

Applicant argues that Brekken is not available as prior art as the claims have been amended so that a priority date of April 28, 1999 may be accorded to claims, as discussed above. Applicant further argues that Melton and Presta each teach away from the proposed combination, as discussed above, and that neither the '538 patent nor the '002 patent cure the deficiencies in the primary references.

Applicant's arguments have been considered but have not been found to be persuasive for the reasons discussed in Section 4 above.

6. All other objections and rejections recited in the previous Office Action are hereby withdrawn.

7. It is noted the previously stated rejection of claims

8. No claims are allowed.

9. **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE

MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8700.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Karen A. Canella/

Ph.D., Primary Examiner, Art Unit 1643

Catherine M. Joyce
Examiner
Art Unit 1642